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Original article

Impact of preprocedural high-sensitive C-reactive protein levels on long-term clinical outcomes of patients with stable coronary artery disease and chronic kidney disease who were treated with drug-eluting stents

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ABSTRACT

Background: To evaluate the prognostic impact of preprocedural high-sensitivity C-reactive protein (hsCRP) levels on the long-term clinical outcomes after first-generation drug-eluting stent (DES) implantation in chronic kidney disease (CKD) patients with stable coronary artery disease (CAD).

Methods and results: We found significant interaction between CKD and hsCRP levels ($p = 0.0138$) in 1176 consecutive patients with stable CAD who were treated with first-generation DES implantation between 2004 and 2009 at our institution. Therefore, we separately analyzed data from patients with and without CKD who were assigned to tertiles based on preprocedural hsCRP levels. We evaluated the incidence of major adverse cardiovascular events (MACE) comprising all-cause death, nonfatal myocardial infarction, and target vessel revascularization after percutaneous coronary intervention during a median follow-up period of 1266 days. The rate of MACE significantly differed among the tertiles (log-rank $p = 0.0074$) in the group with CKD. Multivariate Cox regression analysis significantly associated a higher hsCRP tertile with MACE in the CKD group (hazard ratio 2.39, 95% confidence interval 1.27–4.75, $p = 0.0062$).

Conclusion: Elevated preprocedural serum hsCRP levels might be associated with the long-term clinical outcomes of patients with stable CAD and CKD who were implanted with first-generation DES.

Introduction

Atherosclerosis is fundamentally an inflammatory disease and C-reactive protein (CRP) is an inflammatory biomarker that is an independent predictor of adverse cardiovascular events in patients with coronary artery disease (CAD) [1–4]. In addition, CRP is an independent predictor of short-term adverse outcomes after percutaneous coronary intervention (PCI) using bare metal stents (BMS) [5]. The introduction of drug-eluting stents (DES) considerably reduced restenosis rates [6,7], but restenosis remains a major problem in some populations of patients such as those with diabetes or renal impairment [8]. The predictive value of CRP for long-term outcomes in these populations has not been fully evaluated and remains controversial [9,10].

Chronic kidney disease (CKD) is an established risk factor for the development of cardiovascular disease [11,12] and a potent predictor of adverse clinical outcomes despite PCI with balloon angioplasty or BMS [13,14]. Furthermore, restenosis and adverse clinical outcomes remain major issues for patients with CKD including those implanted with DES [8]. CKD is a result of a combination of atherosclerosis that is accelerated through the promotion of oxidative stress, endothelial dysfunction, and vascular inflammation [15,16]. Thus, CKD per se might play major roles in the development and progression of atherosclerosis and related adverse clinical events, and in the development of restenosis after PCI with DES. From this perspective, the presence

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or absence of CKD might affect the ability of CRP to predict clinical outcomes after PCI with DES.

The present study evaluates whether interactions between CKD and CRP levels affect long-term clinical outcomes in patients with stable CAD who were implanted with first-generation DES.

Methods

Study population and data collection

This is a single-center, observational study of data from patients who underwent scheduled PCI between August 2004 when DES were adopted at Juntendo University Hospital and December 2009. Only the data from patients with stable CAD were assessed. Patients with acute coronary syndrome (ACS) including unstable angina pectoris (UAP) and acute myocardial infarction (AMI) were excluded. In addition, patients with known malignancies, active inflammatory diseases, and those with CKD stage 5 or receiving dialysis therapy were also excluded [17]. We defined CKD as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, and calculated the eGFR based on the modification of diet in renal disease equation modified with a Japanese coefficient using baseline serum creatinine [18].

Demographic data as well as information about coronary risk factors and medications were extracted from our institutional database. Blood samples were collected in the early morning after an overnight fast and blood pressure (BP) was measured at the time of admission. Patients with BP $>$ 140/90 mmHg or under anti-hypertensive medication were regarded as being hypertensive. Dyslipidemia was defined as low-density lipoprotein cholesterol (LDL-C) $\geq$ 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) $\leq$ 40 mg/dL, triglyceride (TG) $\geq$ 150 mg/dL and being treated with statins and/or lipid-lowering agents [19]. Diabetes mellitus was defined as either hemoglobin A1c (HbA1c) $\geq$ 6.5% or under medication with insulin or oral hypoglycemic drugs. The estimated HbA1c (%) was calculated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) using the formula HbA1c (%) = 1.02 $\times$ HbA1c (JDS; %) + 0.25% [20]. We

Table 1
Baseline clinical characteristics of the study population.

	Overall (n = 1176)	Lowest tertile T1 (n = 393) <0.049 mg/dL	Middle tertile T2 (n = 391) 0.050–0.163 mg/dL	Highest tertile T3 (n = 392) >0.164 mg/dL	p-Value
Age	66.5 ± 9.4	66.0 ± 9.1	66.5 ± 8.9	66.9 ± 10.2	0.41
Male, n (%)	968 (84.0)	330 (84.0)	337 (86.2)	321 (81.9)	0.26
Hypertension, n (%)	892 (75.9)	285 (72.5)	308 (78.8)	299 (76.3)	0.12
Dyslipidemia, n (%)	928 (78.9)	309 (78.6)	312 (79.8)	307 (78.3)	0.87
Diabetes, n (%)	588 (50.0)	191 (48.6)	201 (51.4)	196 (50.0)	0.73
Current smoking, n (%)	258 (21.9)	72 (18.3)	71 (18.1)	115 (29.4)	<0.0001
Family history, n (%)	365 (31.0)	127 (32.3)	115 (29.4)	123 (31.4)	0.67
Multivessel Disease, n (%)	825 (70.3)	268 (68.2)	267 (68.3)	290 (74.4)	0.10
Prior MI, n (%)	319 (28.7)	109 (29.4)	102 (27.6)	108 (29.3)	0.83
Prior CABG, n (%)	119 (10.7)	31 (8.4)	47 (12.7)	41 (11.1)	0.15
Prior PCI, n (%)	431 (38.8)	152 (41.0)	144 (38.9)	135 (36.6)	0.47
LVEF	61.9 ± 11.0	62.5 ± 9.8	62.4 ± 10.9	60.6 ± 12.1	0.12
BMI, kg/m^2	24.5 ± 3.2	24.0 ± 2.9	24.6 ± 2.9	24.9 ± 3.6	0.0015
Waist circumference, cm	88.0 ± 8.5	86.2 ± 8.1	88.7 ± 8.2	89.2 ± 8.8	<0.0001
SBP, mmHg	130.6 ± 19.9	129.4 ± 20.6	131.6 ± 18.3	130.8 ± 20.3	0.10
DBP, mmHg	70.0 ± 12.0	70.1 ± 11.7	70.3 ± 11.8	69.7 ± 12.5	0.85
LDL-C, mg/dL	107.3 ± 30.3	104.5 ± 29.2	106.5 ± 30.4	111.0 ± 30.9	0.03
HDL-C, mg/dL	44.0 ± 11.6	46.2 ± 11.8	44.1 ± 11.0	41.8 ± 11.6	<0.0001
TG, mg/dL	140.4 ± 70.7	129.4 ± 63.3	146.9 ± 72.3	145.1 ± 75.0	0.0001
FBG, mg/dL	109.7 ± 32.9	105.9 ± 32.0	112.6 ± 36.1	110.5 ± 34.5	0.0014
HbA1c, %	6.06 ± 1.18	6.02 ± 1.19	6.10 ± 1.22	6.11 ± 1.15	0.17
eGFR, mL/min/1.73 m^2	69.1 ± 16.7	69.9 ± 15.9	69.1 ± 16.9	68.0 ± 17.1	0.19
CKD staging					0.45
Stage 1, n (%)	119 (10.1)	43 (10.9)	39 (10.0)	37 (9.4)	
Stage 2, n (%)	696 (59.2)	242 (61.6)	226 (57.8)	228 (58.2)	
Stage 3, n (%)	355 (30.2)	107 (27.2)	125 (31.9)	123 (31.4)	
Stage 4, n (%)	6 (0.5)	1 (0.25)	1 (0.3)	4 (1.0)	
Medication					
Aspirin, n (%)	1163 (99.2)	389 (99.5)	386 (99.0)	388 (99.2)	0.71
Thienopyridines, n (%)	1150 (98.1)	384 (98.2)	381 (98.7)	385 (98.5)	0.72
Ca-blockers, n (%)	506 (43.2)	165 (42.2)	183 (46.9)	158 (40.4)	0.17
ACE inhibitors, n (%)	154 (13.1)	50 (12.8)	47 (12.1)	57 (14.6)	0.56
ARBs, n (%)	476 (40.6)	161 (41.2)	157 (40.3)	158 (40.4)	0.96
β-Blockers, n (%)	655 (55.9)	211 (54.0)	222 (56.9)	222 (56.8)	0.64
Statins, n (%)	836 (71.4)	291 (74.4)	273 (70.2)	272 (69.6)	0.26
Culprit of vessel					0.39
LAD, n (%)	508 (43.2)	181 (46.1)	167 (42.7)	155 (39.5)	
LCX, n (%)	282 (24.0)	92 (23.4)	90 (23.0)	96 (24.5)	
RCA, n (%)	357 (30.4)	110 (28.0)	115 (29.4)	127 (29.1)	
LMT, n (%)	29 (2.4)	8 (2.0)	14 (3.6)	7 (1.8)	
Type of stents					0.06
SES, n (%)	918 (78.1)	319 (81.2)	308 (78.8)	291 (74.2)	
PES, n (%)	258 (21.9)	74 (18.8)	83 (21.2)	101 (25.8)	

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft surgery; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery LDL-C, low-density lipoprotein cholesterol; LMT, left main trunk; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stents; RCA, right coronary artery; SBP, systolic blood pressure; SES, sirolimus-eluting stents; TG, triglyceride.

measured levels of high-sensitivity CRP (hsCRP) to assess CRP levels.

Written informed consent was obtained from all patients before undergoing coronary intervention. This study proceeded under the approval from our institutional review board in accordance with the Declaration of Helsinki.

Primary endpoint

The primary outcome was major adverse cardiac events (MACE) defined as a composite of all-cause death, ACS, and target vessel revascularization (TVR). Clinical follow-up comprised analyses of office visit charts and responses to questionnaires sent to patients or their families and telephone contact. MACE that occurred during the initial hospitalization were excluded. Mortality data were collected from the medical records of patients who died or who were treated at our institution and details and causes of death were obtained from other hospitals where patients had been admitted. We defined ACS as unstable angina (UAP), non-ST segment elevation myocardial infarction (NSTEMI), or STEMI. UAP was diagnosed as having angina at rest or in an accelerating pattern with negative cardiac biomarkers, with or without electrocardiogram (ECG) changes indicative of myocardial ischemia. We defined myocardial infarction as troponin T positivity. TVR was considered to be ischemia-driven if associated with a target vessel diameter stenosis of $\geq$75% with ischemic symptoms, or a target vessel diameter stenosis of $\geq$90% with or without documented ischemia.

Statistical analysis

Quantitative data are expressed as means $\pm$ SD and categorical variables are presented as frequencies. Patients were assigned to tertiles based upon preprocedural hsCRP values. Continuous variables across tertiles were compared using a one-way ANOVA or the Kruskal–Wallis test. Categorical variables were compared using chi-square statistics. Unadjusted cumulative event rates were estimated using Kaplan–Meier curve and compared across tertiles. The effects of hsCRP levels on MACE after PCI were determined using multivariable Cox proportional hazard regression analysis. Age, gender, body mass index (BMI), waist circumference, hypertension, diabetes, current smoking, family history of CAD, CKD, prior myocardial infarction, left ventricular ejection fraction (LVEF), triple vessel disease, type C lesion, stent size, stent length, type of DES, and medication with statins and angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARB) were selected as covariates from among the baseline variables. To assess whether potential relationships between hsCRP levels and MACE were affected by any other covariates, we conducted Cox proportional hazard regression with an interaction term between hsCRP levels and other covariates. Thereafter, covariates with $p < 0.05$ in univariable analysis were selected for multivariable analysis. Levels of hsCRP were included in multivariate model, and hazard ratios (HRs) and confidence intervals (CIs) were calculated. We determined whether the results differed from the cut-off points using secondary analyses in which hsCRP levels were treated as a natural logarithm-transformed continuous variable. Values with $p < 0.05$ were considered to indicate statistically significant difference. All data were analyzed using JMP version 9.0 for Windows (SAS Institute, Cary, NC, USA).

Results

During the study period, 1218 patients underwent scheduled PCI with first-generation DES. Among them, we finally analyzed data from 1176 eligible patients with stable CAD who were treated with the first-generation DES. Table 1 shows the baseline characteristics of subjects according to the hsCRP tertiles. The median follow-up period was 1266 days (interquartile range, 675–1751 days) and prognostic data were fully documented during the entire follow-up period. There were 197 (16.8%) MACEs including 23 (2.0%) deaths, 64 (5.4%) ACS, and 110 (9.4%) TVR. Fig. 1 shows the cumulative event-free survival curves for MACE according to hsCRP tertiles. The curves of each tertile significantly differed (log-rank test, $p = 0.002$). Risk analyses using Cox proportional-hazard models revealed a significant interaction between hsCRP levels and the presence or absence of CKD ($p = 0.0138$). Therefore, we separately analyzed the presence ($n = 361$) or absence ($n = 815$) of CKD.

Tables 2 and 3 show baseline clinical characteristics across hsCRP tertiles of patients with and without CKD. Current smoking, metabolic factors including BMI, waist circumference, HDL-C, and triglycerides significantly differed across tertiles in the group without CKD, whereas only age significantly differed across tertiles in the group with CKD. A comparison of angiographic and procedural characteristics compared across tertiles in each group found no significant differences across hsCRP tertiles in the group with and without CKD.

Figs. 2 and 3 show Kaplan–Meier survival curves for MACE stratified according to tertiles of preprocedural hsCRP levels in patients with and without CKD, respectively. Rates of MACE among tertiles ($p = 0.17$) did not significantly differ in the group without CKD, whereas the cumulative incidence of events significantly increased with increasing hsCRP levels in the group with CKD ($p = 0.0074$). Table 4 summarizes the findings of univariate and multivariate Cox hazard regression analyses. Variables with $p < 0.05$ in univariable analysis comprised triple vessel disease, stent length, and type C lesions in the group without CKD, and age, type of DES, and type C lesions in the group with CKD. Even after adjustment for other covariates, hsCRP levels remained significantly associated with MACE only in the group with CKD.

Discussion

This observational study found interaction between CKD and the impact of preprocedural hsCRP on long-term clinical outcomes. Preprocedural hsCRP levels were associated with poor outcomes after PCI with first-generation DES only in the patients with CKD. These findings suggest that preprocedural hsCRP levels affect the

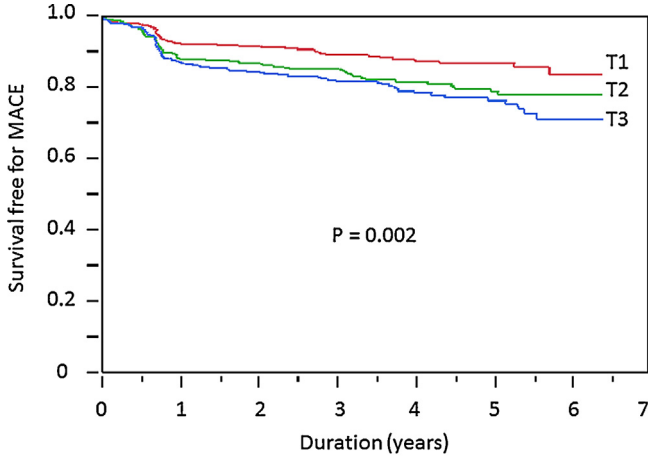

Fig. 1. Kaplan–Meier curves for major adverse cardiovascular events (MACE) in all patients.

Table 2
Baseline clinical characteristics in patients without CKD.

	Lowest tertile T1 ($n=269$) <0.046 mg/dL	Middle tertile T2 ($n=274$) 0.047–0.155 mg/dL	Highest tertile T3 ($n=272$) >0.156 mg/dL	p-Value
Age	65.1 ± 9.2	64.8 ± 8.7	64.4 ± 9.9	0.71
Male, *n* (%)	224 (83.3)	238 (86.9)	225 (82.7)	0.35
Hypertension, *n* (%)	196 (72.9)	212 (77.4)	204 (75.0)	0.48
Dyslipidemia, *n* (%)	212 (78.8)	210 (76.6)	213 (78.3)	0.82
Diabetes, *n* (%)	132 (49.1)	136 (49.6)	135 (49.6)	0.99
Current smoking, *n* (%)	56 (20.8)	53 (19.3)	87 (32.0)	<0.01
Family history, *n* (%)	87 (32.3)	81 (29.6)	87 (32.0)	0.75
Multivessel disease, *n* (%)	175 (65.1)	171 (62.4)	201 (73.9)	0.012
Prior MI, *n* (%)	70 (26.0)	75 (27.4)	78 (28.7)	0.78
Prior CABG, *n* (%)	22 (8.2)	28 (10.2)	28 (10.3)	0.63
Prior PCI, *n* (%)	96 (35.7)	93 (33.9)	92 (33.8)	0.88
LVEF	62.5 ± 10.2	62.2 ± 11.1	61.5 ± 10.7	0.53
BMI, kg/m^2	23.9 ± 2.9	24.7 ± 3.0	24.9 ± 3.8	<0.01
Waist circumference, cm	85.6 ± 7.9	88.5 ± 8.6	89.2 ± 9.1	<0.01
SBP, mmHg	129.1 ± 20.3	130.4 ± 17.2	129.8 ± 20.7	0.74
DBP, mmHg	69.9 ± 11.7	70.5 ± 11.3	70.0 ± 13.2	0.80
LDL-C, mg/dL	105.0 ± 29.5	108.7 ± 29.5	111.1 ± 30.7	0.06
HDL-C, mg/dL	46.7 ± 11.6	44.3 ± 10.9	41.7 ± 10.9	<0.01
TG, mg/dL	129.4 ± 65.7	144.4 ± 65.9	148.4 ± 80.2	<0.01
FBG, mg/dL	108.3 ± 34.7	111.3 ± 30.3	112.7 ± 33.4	0.014
HbA1c, %	6.11 ± 1.30	6.09 ± 1.23	6.09 ± 1.13	0.50
eGFR, mL/min/1.73 m^2	76.8 ± 12.6	77.2 ± 14.3	76.4 ± 13.3	0.82
CKD staging				0.94
Stage 1, *n* (%)	40 (14.9)	41 (15.0)	38 (14.0)	
Stage 2, *n* (%)	229 (85.1)	233 (85.0)	234 (86.0)	
Medication				
Aspirin, *n* (%)	268 (100)	272 (99.3)	271 (100)	0.14
Thienopyridines, *n* (%)	265 (98.9)	268 (97.8)	267 (98.5)	0.24
Ca-blockers, *n* (%)	110 (41.0)	123 (44.9)	105 (38.8)	0.34
ACE inhibitors, *n* (%)	31 (11.6)	37 (13.5)	40 (14.8)	0.55
ARBs, *n* (%)	101 (37.7)	108 (39.4)	106 (39.1)	0.91
β-Blockers, *n* (%)	144 (53.7)	151 (55.1)	160 (59.0)	0.44
Statins, *n* (%)	202 (75.4)	189 (69.2)	192 (70.9)	0.26
Target lesion, *n* (%)				0.43
LMT	5 (1.9)	9 (3.3)	4 (1.5)	
LAD	121 (45.0)	120 (43.8)	108 (39.7)	
LCX	66 (24.5)	64 (23.4)	65 (23.9)	
RCA	77 (28.6)	81 (29.6)	94 (34.6)	
Type C, *n* (%)	144 (53.5)	149 (54.4)	152 (55.9)	0.86
LVEF, %	62.5 ± 10.2	62.2 ± 11.1	61.5 ± 10.7	0.53
Reference lumen diameter, mm	2.70 ± 0.41	2.73 ± 0.42	2.76 ± 0.45	0.20
Minimum lumen diameter, mm				
At pre-procedure	0.44 ± 0.35	0.45 ± 0.35	0.43 ± 0.28	0.98
At post-procedure	2.62 ± 0.45	2.70 ± 0.43	2.70 ± 0.45	0.10
Type of stent				0.13
SES use, *n* (%)	199 (74.0)	214 (78.1)	192 (70.6)	
PES use, *n* (%)	70 (26.0)	60 (21.9)	80 (29.4)	
Number of stent, *n*	1.4 ± 0.6	1.3 ± 0.6	1.4 ± 0.6	0.16
Mean stent size, mm	2.87 ± 0.37	2.88 ± 0.36	2.89 ± 0.38	0.69
Total stent length, mm	28.5 ± 16.5	28.7 ± 15.4	30.0 ± 16.3	0.42

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft surgery; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery LDL-C, low-density lipoprotein cholesterol; LMT, left main trunk; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stents; RCA, right coronary artery; SBP, systolic blood pressure; SES, sirolimus-eluting stents; TG, triglyceride.

long-term clinical outcomes of patients with stable CAD after PCI with first-generation DES implantation only when CKD co-exists.

Elevated preprocedural CRP levels are powerful predictors of adverse clinical cardiovascular events after BMS [5,21]. The predictive value of CRP for clinical outcomes after PCI in the DES era has remained controversial [9,22]. Park et al. found that preprocedural CRP did not predict restenosis after DES implantation [9]. However, the absence of a relationship between preprocedural hsCRP levels and clinical outcomes in their study might be explained by the fact that half of the patients included in their study had ACS. Indeed, another previous study of patients without myocardial infarction identified preprocedural CRP as an independent predictor of two-year clinical outcomes after PCI including death and myocardial infarction [23]. The present study did not include patients with ACS to exclude the confounding effect of myocardial necrosis on preprocedural CRP which can interfere with the ability to detect potential of vascular inflammation. In fact, we found a similar univariable relationship between preprocedural hsCRP levels and MACE after PCI with first-generation DES. The present study also found an interaction between CKD and hsCRP was associated with outcome. This might partially explain the conflicting results of previous studies that have assessed the prognostic impact of preprocedural hsCRP levels after PCI with DES.

Renal dysfunction is closely associated with systemic atherosclerosis, which increases risk for cardiovascular events even in

Table 3
Baseline clinical characteristics in patients with CKD.

	Lowest tertile T1 ($n=120$) <0.058 mg/dL	Middle tertile T2 ($n=119$) 0.058–0.189 mg/dL	Highest tertile T3 ($n=122$) >0.189 mg/dL	p-Value
Age	68.8 ± 8.6	70.4 ± 7.9	71.6 ± 9.4	<0.05
Male, *n* (%)	100 (83.3)	103 (86.6)	98 (80.3)	0.43
Hypertension, *n* (%)	88 (73.3)	96 (80.7)	96 (78.7)	0.37
Dyslipidemia, *n* (%)	94 (78.3)	103 (86.6)	96 (78.7)	0.17
Diabetes, *n* (%)	58 (48.3)	62 (52.1)	60 (49.2)	0.83
Current smoking, *n* (%)	16 (13.3)	18 (15.1)	28 (23.0)	0.11
Family history, *n* (%)	37 (30.8)	35 (29.4)	38 (31.2)	0.95
Multivessel disease, *n* (%)	48 (78.7)	52 (83.9)	50 (84.7)	0.64
Prior MI, *n* (%)	36 (36.7)	29 (30.2)	31 (30.7)	0.56
Prior CABG, *n* (%)	9 (9.2)	18 (18.8)	14 (13.9)	0.15
Prior PCI, *n* (%)	53 (54.1)	52 (54.2)	45 (44.6)	0.30
LVEF	62.7 ± 8.8	63.2 ± 10.7	58.6 ± 14.8	0.09
BMI, kg/m^2	24.1 ± 2.9	24.5 ± 2.8	24.8 ± 3.3	0.37
Waist circumference, cm	87.3 ± 8.6	88.7 ± 7.6	89.4 ± 8.0	0.14
SBP, mmHg	131.9 ± 21.9	132.0 ± 21.6	133.3 ± 19.2	0.70
DBP, mmHg	71.6 ± 12.3	68.3 ± 11.8	69.6 ± 11.2	0.13
LDL-C, mg/dL	104.1 ± 28.6	101.3 ± 30.8	110.0 ± 32.7	0.19
HDL-C, mg/dL	45.4 ± 12.5	42.8 ± 10.9	42.4 ± 13.1	0.06
TG, mg/dL	133.1 ± 67.4	146.3 ± 69.9	139.4 ± 71.0	0.18
FBG, mg/dL	104.2 ± 32.9	110.5 ± 41.6	106.7 ± 37.2	0.29
HbA1c, %	5.89 ± 0.98	5.91 ± 0.99	6.17 ± 1.20	0.24
eGFR, mL/min/1.73 m^2	52.0 ± 6.9	52.0 ± 7.6	50.7 ± 8.1	0.41
CKD staging				0.60
Stage 3, *n* (%)	119 (99.2)	117 (98.3)	119 (97.5)	
Stage 4, *n* (%)	1 (0.8)	2 (1.7)	3 (2.5)	
Medication				
Aspirin, *n* (%)	118 (99.2)	116 (98.3)	122 (100)	0.68
Thienopyridines, *n* (%)	116 (97.5)	114 (96.6)	120 (98.3)	0.43
Ca-blockers, *n* (%)	55 (46.2)	59 (50.0)	54 (44.3)	0.66
ACE inhibitors, *n* (%)	18 (15.1)	12 (10.2)	16 (13.1)	0.51
ARBs, *n* (%)	54 (45.4)	53 (44.9)	54 (44.3)	0.98
β-Blockers, *n* (%)	64 (53.8)	72 (61.0)	64 (52.5)	0.36
Statins, *n* (%)	82 (68.9)	86 (72.9)	85 (69.7)	0.77
Target lesion, *n* (%)				0.55
LMT	3 (2.5)	5 (4.2)	3 (2.5)	
LAD	57 (47.5)	49 (41.2)	51 (41.8)	
LCX	28 (23.3)	28 (23.5)	32 (26.2)	
RCA	32 (26.7	37 (31.1)	36 (29.5)	
Type C, *n* (%)	60 (50.0)	70 (58.8)	75 (61.5)	0.17
Reference lumen diameter, mm	2.72 ± 0.43	2.73 ± 0.41	2.76 ± 0.43	0.77
Minimum lumen diameter, mm				
At pre-procedure	0.45 ± 0.32	0.51 ± 0.30	0.50 ± 0.38	0.40
At post-procedure	2.63 ± 0.40	2.67 ± 0.43	2.68 ± 0.37	0.53
Type of stent				0.28
SES use, *n* (%)	95 (79.2)	84 (70.6)	94 (77.1)	
PES use, *n* (%)	25 (20.8)	35 (29.4)	28 (22.9)	
Number of stent, *n*	1.4 ± 0.7	1.3 ± 0.7	1.3 ± 0.5	0.71
Mean stent size, mm	2.86 ± 0.35	2.88 ± 0.36	2.90 ± 0.33	0.75
Total stent length, mm	28.0 ± 16.2	28.8 ± 15.5	27.4 ± 14.0	0.78

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft surgery; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery LDL-C, low-density lipoprotein cholesterol; LMT, left main trunk; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stents; RCA, right coronary artery; SBP, systolic blood pressure; SES, sirolimus-eluting stents; TG, triglyceride.

patients with less severe forms such as CKD [24]. CKD is also associated with endothelial dysfunction [25] and pronounced neointimal hyperplasia after coronary stenting that leads to more in-stent restenosis. Despite obvious reduction in the restenosis rate due to DES implantation, renal dysfunction and/or CKD are still associated with poor adverse clinical outcomes including all-cause death, myocardial infarction, and angiographic restenosis [26–28]. CKD has been described as a state of accelerated atherosclerosis through several pathways including enhanced vascular inflammation [15,16]. We found interactions between presence or absence of CKD and preprocedural inflammatory status in the vasculatures as well as clinical outcomes. Even after adjustment for other covariates, the significant association between preprocedural hsCRP levels and long-term clinical outcomes in patients with stable CAD with CKD persisted. Choi et al. similarly found that poor renal function and high hsCRP levels were additively associated with mortality and myocardial infarction in an unselected population that was treated by PCI with DES [29]. In addition, a previous study demonstrated the prognostic impact of CRP levels on clinical outcome after implantation of sirolimus-eluting stents in patients on hemodialysis [30]. Elevated CRP levels are associated with major adverse outcomes including cardiovascular death, non-fatal myocardial infarction, and target lesion revascularization which is similar to the result of the present study suggesting that increased preprocedural CRP values predict the adverse outcomes after DES implantation in patients with CKD.

Several limitations of the present study require consideration. This single-center, observational study included a small sample

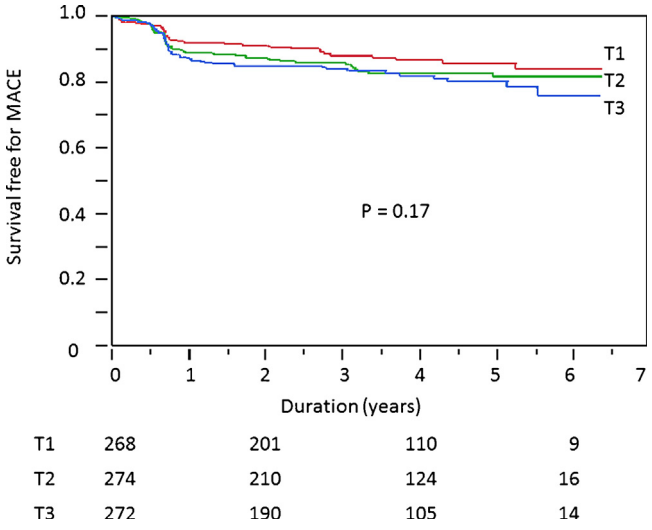

Fig. 2. Kaplan–Meier curves for major adverse cardiovascular events (MACE) in patients without chronic kidney disease.

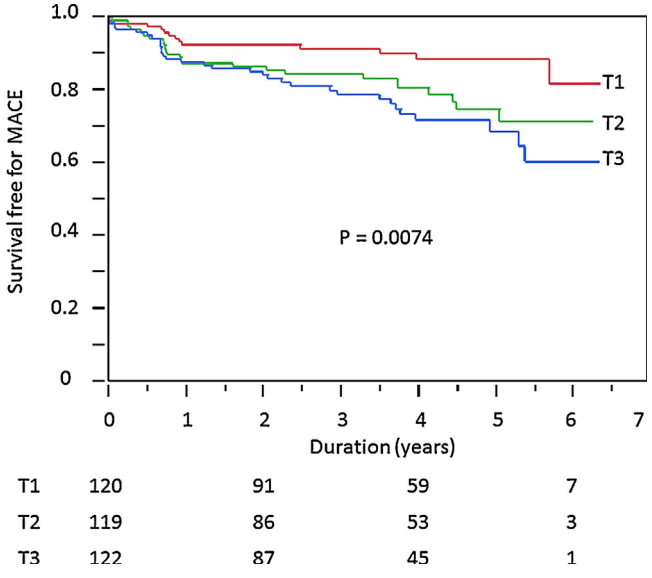

Fig. 3. Kaplan–Meier curves for major adverse cardiovascular events (MACE) in patients with chronic kidney disease.

Table 4
Cox proportional hazards model for MACE.

	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
hsCRP (lowest tertile as reference)						
(a) Patients without CKD						
Middle tertile	1.29	0.83–2.05	0.26	1.26	0.80–1.99	0.32
Highest tertile	1.51	0.97–2.37	0.07	1.43	0.92–2.25	0.11
(b) Patients with CKD						
Middle tertile	2.06	1.07–4.16	0.03	1.86	0.97–3.76	0.06
Highest tertile	2.71	1.46–5.36	0.0014	2.39	1.27–4.75	0.0062

Adjusted for variables were age, gender, body mass index, waist, hypertension, diabetes, current smoking, family history of coronary artery disease, prior myocardial infarction, left ventricular ejection fraction, triple vessel disease, type C lesion, stent size, stent length, type of drug-eluting stent, use of statin and use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. The latter covariates were added in this model if only they were statistically significant predictors of MACE ($p < 0.05$).
MACE, major adverse cardiovascular event; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; hsCRP, high sensitivity C-reactive protein.

cohort, and other unknown confounding factors might have affected outcomes regardless of adjustments in the statistical analyses. In addition, the number of events in the present study was relatively small which led to the absence of statistically significant differences in outcome measures. In fact, hsCRP levels tended to be associated with clinical outcomes in the patients without CKD, but the difference did not reach statistical significance because the cumulative event rate was lower than that of the patients with CKD. Thus, an observational study of a larger cohort is necessary. In the present study, follow-up angiography was performed in 158 (86.6%) patients which is a relatively high percentage. Routine angiographic follow-up after implantation of DES may increase revascularization of non-ischemic lesions due to the so-called oculostenotic reflex but has no impact on long-term outcomes [31]. Since we defined CKD as eGFR < 60 mL/min/1.73 m^2 in the absence of information about proteinuria and structural kidney disease, some patients might have been misclassified. Finally, we had no information about the patient compliance with the prescribed medical therapy during follow-up.

In conclusion, elevated preprocedural serum hsCRP levels are associated with long-term clinical outcomes in stable CAD patients with CKD and might be useful to predict long-term adverse events after first-generation DES implantation in patients with CKD.

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Conflict of interest

The authors declare that there is no conflict of interest.

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